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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/519,959	03/07/2000	Nancy Carrasco	96700/488	9663

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 12/13/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/519,959	CARRASCO ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed on October 3, 2001 in Paper No. 11 is acknowledged and has been entered. Claims 12-28 have been canceled. Claims 1, 3, and 7 have been amended.

2. Claims 1-11 are pending in the application and are currently under prosecution.

Oath/Declaration

3. The copies of the declaration, which were filed on November 29, 2000, are sufficient to overcome the defect in the original declaration. In response to the previous Office Action, Applicants have submitted a second set of the copies in Paper No. 10, which was filed on October 3, 2001.

Claim Rejections Maintained and Response to Applicants' Remarks

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 are indefinite because there is no positive correlation step which clearly relates back to the preamble of claim 1. Amending claim 1 to recite, for example, the phrase "whereby the subject is diagnosed with breast cancer" in the last line can obviate this rejection.

Claims 7-9 are also indefinite because claim 7 recites the term "hybridizes". While the Examiner appreciates Applicants' endeavor to resolve the issue raised in the previous Office Action by amending claim 7 to recite "specifically and selectively hybridizes" since as amended, it is clear that the probe must hybridize specifically and

selectively to the nucleic acid encoding mgNIS; however, as stated in the previous Office Action, hybridization conditions, which would necessarily be chosen at the discretion of the investigator since the claim does not refer to specific conditions, are highly variable and can provide very different results. Depending upon the hybridization conditions, which may range from highly permissive to highly stringent, a given probe might hybridize to a multitude of homologous nucleic acid sequences, many of which would not encode mgNIS. Therefore, one of ordinary skill in the art would not reasonably apprised of the metes and bounds of the invention. Amending claim 7 to recite the specific conditions under which the claim requires the probe to specifically and selectively hybridize to the nucleic acid encoding mgNIS could obviate this rejection. However, again, Applicant is cautioned against the addition of new matter to the claims.

In summary, Applicants' arguments have been carefully considered but have not been found persuasive. Accordingly, the rejection of claims 1-11 under 35 USC § 112, second paragraph for the reason set forth in the previous Office Action is maintained.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 2, 10, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Cancroft, et al (*Radiology* **106**: 441-444, 1973; Form PTO-1449, citation 1), as evidenced by Socolow, et al (*Endocrinology* **80**: 337-344, 1967), Tazebay, et al (*Nature Medicine* **6**: 871-878, 2000), and Spitzweg, et al (*Journal of Clinical Endocrinology* **83**: 1746-1751, 1998; Form PTO-1449, citation 25) for the reason stated in the previous Office Action.

The claims are drawn to a method of diagnosing breast cancer in a non-lactating subject, said method comprising determining the expression of mammary gland

sodium/iodide symporter in the breast tissue of the subject (claim 1), wherein detection of expression of mgNIS in the breast tissue is indicative of breast cancer in the subject and failure to detect the expression of mgNIS in the breast tissue is indicative of the absence of breast cancer in the subject, wherein the expression of the symporter is detected *in vitro* or *in vivo* (claim 2) using a detectable agent that is selectively taken up by the symporter (claim 10) wherein the agent is radioiodide or ^{99m}Tc-pertechnetate (claim 11).

Applicants traverse the rejection of claims 1, 2, 10, and 11 arguing, "Cancroft *et al.* did not establish a method for diagnosing breast cancer; at most, Cancroft *et al.* taught a method for differentiating benign and malignant breast masses" (page 4, paragraph 2). In response, according to The On-line Medical Dictionary© (Academic Medical Publishing & CancerWEB, 1997-98), the term "diagnosis" is defined as "The determination of the nature of a case of disease". As Applicants have stated, Cancroft, et al teach a method for differentiating benign and malignant masses in the breast tissue of a subject. Accordingly, the teachings of Cancroft, et al anticipate the claimed invention since the goal of the diagnostician is to procure a differential diagnosis of the patient's pathology, i.e., make a "determination of which two or more diseases with similar symptoms is the one from which a patient is suffering from based on an analysis of the clinical data" (The On-line Medical Dictionary©).

Additionally, Applicants state, "the method of the claimed invention requires that detection of expression of mgNIS in breast tissue of a subject" be indicative of breast cancer in the subject, but argue, "Cancroft *et al.* did not teach or suggest that mgNIS expression is detectable in breast cancer tissue, but not in normal, non-lactating breast tissue" (paragraph bridging pages 4 and 5). While the meaning of the latter argumentative statement is somewhat uncertain, presumably Applicant contends that Cancroft, et al did not explicitly teach that their method for diagnosis requires the detection of expression of mgNIS. However, as stated in the previous Office Action:

> While Cancroft, et at teach that the mechanism of ^{99m}Tc-pertechnetate concentration in malignant breast masses is not clear, it is an inherent feature of ^{99m}Tc-pertechnetate to concentrate in the malignant breast masses by a mechanism involving its selective

> uptake by NIS, as evidenced by Socolow, et al and Spitzweg, et al. In the method of Cancroft, et al, the level of ^{99m}Tc-pertechnetate taken up by a cancer cells reflects the level of expression in the cells of mgNIS, which is responsible for the uptake of ^{99m}Tc-pertechnetate. Therefore, the level of radioactivity detected in the cells is a measure of the level of mgNIS expression in the subject's breast cancer cells; thus, the diagnostic method of Cancroft, et al intrinsically detects the expression of mgNIS in the cancer cells (paragraph bridging pages 5 and 6).

For clarification, if the breast cancer cells of the subject take up ^{99m}Tc-pertechnetate, then necessarily active mgNIS is expressed in those cells. If mgNIS is expressed and active in the breast cancer cells of the subject, then those cells will take up ^{99m}Tc-pertechnetate. Moreover, if the breast tissue of the subject takes up ^{99m}Tc-pertechnetate, the method of Cancroft, et al "detects the expression of mgNIS" in the breast tissue and provides a definitive diagnosis of breast cancer in the subject. On the other hand, if the breast tissue of the subject fails to take up ^{99m}Tc-pertechnetate, the method of Cancroft, et al fails to detect the expression of mgNIS in the breast tissue and indicates the absence of breast cancer in the subject. Therefore, as stated in the previous Office Action, the method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering ^{99m}Tc-pertechnetate to a subject that is to be diagnosed with breast cancer and thereby determining whether or not mgNIS is expressed in the subject's breast tissue. Thus, the claimed method is anticipated because the prior art method will inherently lead to conferring a diagnosis of breast cancer in the subject. See *Ex parte Novitski* 26 USPQ 1389 (BPAI 1993).

Additionally, it is noted that the limitation recited in the amended claims requires the method to be practiced with a non-lactating subject; however, this limitation is not considered to distinguish the method of the prior art from the method of the claims, because Cancroft, et al did not teach their method could only be used to diagnose breast cancer in a lactating subject. The claimed method is not anticipated by the teachings of Cancroft, et al, because the prior art method will also inherently lead to conferring a diagnosis of breast cancer in a non-lactating subject.

It is noted that Applicants appreciate the inherent properties of mgNIS because the specification discloses, mgNIS is "a glycoprotein that catalyzes the transport of iodide" (page 3, lines 17 and 18). In fact, it is well known in the art that iodide and

^{99m}Tc-pertechnetate are transported into the thyroid by the sodium/iodide symporter and it reasonably follows that iodide and ^{99m}Tc-pertechnetate are also transported by the sodium/iodide symporter of breast tissue (i.e., mgNIS). Still, in the rebuttal of the rejection, Applicants argue, "the inherent characteristics must necessarily flow from the reference's teachings" (page 5, paragraph 2) and since the Examiner cited Socolow, et al, Tazeby, et al, and Spitzweg, et al, Applicants evidently contend that the inherent characteristics of the method of Cancroft, et al do not flow from the reference's teachings. According to the MPEP § 2112, "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). In the instant rejection, the Examiner has provided a basis in fact and technical reasoning to reasonably support the determination that the inherent features of the prior art method flow from the teachings of Cancroft, et al. Nevertheless, a 35 USC § 102 rejection over multiple references has been held to be proper when the extra references are cited to show that a characteristic not disclosed in the reference is, in fact, inherent. See MPEP § 2131.01.

Finally, Applicants state, "The Examiner has not demonstrated that the increased uptake of ^{99m}Tc-pertechnetate in the malignant breast masses described in Cancroft et al. necessarily resulted from mgNIS expression" (page 5, paragraph 2). The office, however, does not have the facilities for examining and comparing the mechanistic features of Applicant's method with those of the method of the prior art in order to establish that the method of the prior art does not possess the mechanistic features as the claimed invention. The prior art method is deemed the same as the method of the instant claims, absent a showing of any differences. In the absence of evidence to the contrary, the burden is upon Applicants to prove that the claimed method is mechanistically different than that taught by the prior art and to establish patentable differences. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Board of Patent Appeals and Interferences).

Therefore, Applicants' arguments have been carefully considered but have not been found persuasive. Accordingly, upon the basis of the preponderance of evidence, the rejection of claims 1, 2, 10, and 11 under 35 USC § 102(b) for the reason set forth in the previous Office Action is maintained.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cancroft, et al (*Radiology* **106**: 441-444, 1973; Form PTO-1449, citation 1) in view of Eskin, et al (*Obstetrics and Gynecology* **44**: 398-402, 1974; Form PTO-1449, citation 9), Kilbane, et al (Spitzweg, et al (*Journal of Clinical Endocrinology* **83**: 1746-1751, 1998; Form PTO-1449, citation 25) and Jhiang, et al (*Endocrinology* **139**: 4416-4419, 1998; Form PTO-1449, citation 11) for the reason set forth in the previous Office Action.

The subject matter of claims 1, 2, 10, and 11 is set forth in the 35 USC § 102(b) rejection above. Claims 3-6 are drawn to a method for diagnosing breast cancer in a subject, as in claim 1, wherein the expression of mgNIS is detected using a detectably labeled reagent that specifically and selectively binds mgNIS, such as an anti-mgNIS antibody. Claims 7-9 are drawn to a method for diagnosing breast cancer in a subject, as in claim 1, wherein the expression of mgNIS is detected using a detectably labeled nucleic acid probe, which specifically and selectively hybridizes to the nucleic acid molecule encoding mgNIS.

In response to Applicant's argument, it is noted that claims 1-11 are rejected under 35 USC § 103(a) in the previous Office Action as being unpatentable over Cancroft, et al in view of Eskin, et al, Spitzweg, et al, and Jhiang, et al. Accordingly, the answer to Applicants apparent query in the summarizing statement is that the invention is unpatentable over the *combination* of the teachings of the cited references. In this

regard, it is noted that Applicant addressed each of the cited references individually, but one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, in response to Applicant's argument that the teachings of Eskin, et al, Spitzweg, et al, and Jhiang, et al cannot overcome the deficiencies of the primary reference, the test for obviousness is not whether the features of the secondary reference may be bodily incorporated into the structure of the primary references; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Therefore, Applicants' arguments have been carefully considered but have not been found persuasive. Accordingly, upon the basis of the preponderance of evidence, the rejection of claims 1-11 under 35 USC § 103(a) for the reason set forth in the previous Office Action is maintained.

Conclusion

10. No claims are allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Art Unit 1642

DONNA WORTMAN
PRIMARY EXAMINER

slr
December 6, 2001